Target controllability in genetic networks of macrophage activation

Giulia Bassignana[1,2], Jennifer Fransson[1], Olivier Colliot[1,2], Violetta Zujovic[1] and Fabrizio De Vico Fallani[1,2]

1. Sorbonne Universites, UPMC Univ Paris 06, Inserm U-1127, CNRS UMR-7225, Institut du Cerveau et de la Moelle Epinière, Hopital Pitié-Salpêtrière, Paris, France
2. Inria Paris, Aramis project-team, Paris, France

Macrophage cells play an important role in the Multiple Sclerosis (MS) disease. They are known to participate both to the degenerative process, myelin destruction, and to the regenerative one, coordinating remyelination. We focused on two activation states of the macropaghes: 'alert', which senses the environment, and 'pro-inflammatory', which is entitled of the cell defense against external agents. The correct genetic activation of macrophage phenotypes permits a correct remyelinating response [1], thus the possibility to steer it towards an healthy state while acting on a limited number of genes (drivers) would be greatly advantageous.

We modeled macrophage activation as a network (Figure 1.a), where N nodes correspond to genes involved in inflammation and directed links correspond to significant influences (inhibition or activation) as retrieved from macrophages.com [2] activation pathways. To enhance interpretation, genes were assigned to four different categories, according to their position inside a cell.

We assumed a linear time invariant dynamics and modeled our problem in a target controllability framework [3]. Each gene is tested as a driver and target nodes are the 19 genes for which the difference in gene expression between the two states of the macropohage cells is most significant ($p < 0.05$) for patients and controls (Figure 1.b). Since computing the rank of the controllability matrix is ill-conditioned for a large network, it was not possible to test all target nodes at the same time. We computed the **target control centrality** as the number of target nodes that can be controlled from a driver node, when the target are chosen as follows:

- *Step 0*: the target set contains the first target node, the target control centrality is zero.
- *Step 1*: build the subgraph to apply the Kalman criterion, nodes accessible from the driver that can reach the target set.
- *Step 2*: check target controllability.
    - If the configuration is not controllable, discard the last target added to the target set and test the successive one;
    - else, include the successive target in the target set and increase by one the target control centrality.
- Repeat steps 1 and 2 until the last target node is tested.

Results showed that the driver nodes *IRF7*, *PRKCD* and *STAT1*, known to be involved in the MS disease [4] and [5], can control up to 7 target nodes. Our work is a preliminary step towards the identification of the genes influencing the inflammatory process of macrophages, which is a crucial mechanism in the MS' disease.
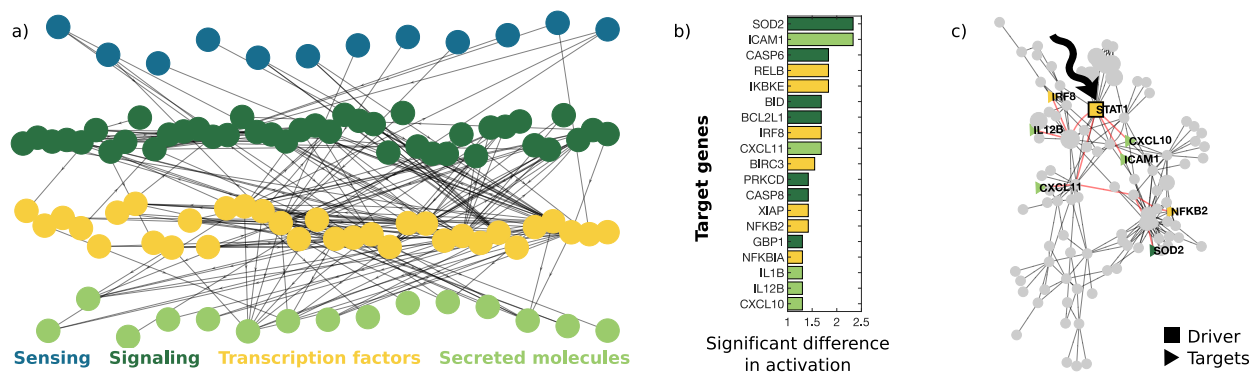

Figure 1: (a) Inferred network of genes involved in phosphorylation, with 101 nodes and 209 directed edges. *Sensing* genes are in the membrane of the cell and start a *signaling* pathway inside the cell, to the *transcription factors* inside the nucleus, which expel *secreted molecules*. (b) Target genes by decreasing significance. (c) Paths from the driver node *STAT1* to its controllable targets.

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